REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The claims have been revised to define the invention with additional clarity. The revisions of claims 1 and 73 find support throughout the application, including in now cancelled claim 7 and at page 23, lines 1-3 and in Example 13. Claims 21 and 26 have been revised to conform with Claim 1, from which they depend (and, in the case of claim 26, to include antecedent basis for the culture medium). Claim 75 has been revised to depend from claim 73. In addition to claim 7, claims 13, 17, 23, 74 and 78 have also been cancelled without prejudice. That the claims have been revised should not be taken as an indication that Applicants agree with any position expressed by the Examiner. Rather, the revisions have been made merely to advance prosecution and Applicants reserve the right to pursue any deleted subject matter in a continuation application.

New claims 80-82 have been added. The new claims find support in the same manner as claim 75 from which they depend and in original claims 11, 14 and 15.

While in no way agreeing with the Examiner's assertion as regards an alleged lack of entitlement of certain of the claims to the priority filing date, that assertion is noted.

Claims 1-5, 7-18, 21-29, 73, 74 and 76-79 stand rejected under 35 USC 112, first paragraph, as allegedly being non-enabled. Withdrawal of the rejection is submitted to be in order in view of the above-noted amendments and further in view of the comments that follow.

Claim 1 as now presented relates to an isolated nucleic acid encoding a chimeric polypeptide, that polypeptide comprising a secretory signal sequence operably linked to human GAA. In accordance with the invention, the secretory signal sequence replaces the leader

sequence of native human GAA. Claim 73 and various claims depending from claims 1 and 73 make reference to specific secretory signal sequences (see, for example, claims 3, 4, 76 and 77) and claims 75 and the new claims depending therefrom make reference to a specific human GAA sequence.

The claims as presented are fully supported by an enabling disclosure and, indeed, nothing in the Examiner comments relating to the claims as previously presented would suggest otherwise. Human GAA has long been known (see first paragraph on page 18 of the subject application and the reference therein to publications dating back to 1988) and the disclosure includes reference to a multitude of suitable secretory signal sequences (see, for example, pages 23-25).

Given the breadth of the disclosure provided, no basis is seen for requiring that the claims be further limited in scope. Any such requirement would unduly restrict Applicants in the scope of protection to which they are rightly entitled given the nature of the subject invention.

In view of the above, withdrawal of the rejection is requested.

Claims 1-5, 7-18, 21-29, 73, 74 and 76-79 stand rejected under 35 USC 112, first paragraph, as allegedly lacking written description. Withdrawal of the rejection is submitted to be in order in view of the above-noted amendments and further in view of the comments that follow.

It is now well settled that:

> The "written description" requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed ..... The written description requirement thus satisfies the policy premises of the

> law, whereby the inventor's technical/scientific advance is added to the body of knowledge, as consideration for the grant of patent exclusivity. The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. .... Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science. (*Underlining added*)

(*Capon v. Eshhar*, 76 USPQ2d 1078 (Fed. Cir. 2005)).

The court's statements in *Capon* are particularly relevant to the instant invention since the claims at issue in *Capon* related to chimeric genes. The court in *Capon* stated that the Board "erred in refusing to consider the state of the scientific knowledge" and pointed out that none of the cases to which the Board attributed the requirement of total DNA re-analysis, e.g., *Regents v. Lilly* (upon which the Examiner relies in rejecting the instant claims), "requires a re-description of what was already known". In *Lilly*, unlike the situation in *Capon* and unlike the situation at hand, the cDNA for human insulin had never been characterized. The *Capon* court went on to point out that the written description requirement "must be applied in the context of the particular invention and the state of the knowledge" (underlining added). The court indicated that the "Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization" (underlining added).

As in *Capon*, Applicants' invention is not in discovering a nucleic acid encoding human GAA or a nucleic acid sequence encoding a secretory signal sequence but in the recited combination of these components to achieve a novel result. Given the nature of the invention, the extensive description provided in the subject application relating to both human GAA and secretory signal sequences, the scientific and technologic knowledge already in existence (note, for example, the references cited in rejecting the claims under 35 USC 102 and 103), no basis is seen for the Examiner's contention that written description is lacking. Accordingly, reconsideration and withdrawal of the rejection are requested.

Claims 1, 2, 5, 7-18 and 21-29 stand rejected under 35 USC 102(b) as allegedly being anticipated by Amilfitano et al. The rejection is traversed.

The claims as now presented require that the secretory signal sequence replace the leader sequence of native human GAA. Amilfitano et al includes no such teaching. Accordingly, withdrawal of the rejection is in order and same is requested.

Claims 1, 2, 5, 7-11, 14, 15, 17 and 21-29 stand rejected under 35 USC 102(b) as allegedly being anticipated by Van Bree et al. The rejection is traversed.

As pointed out above, the claims as now presented require that the secretory signal sequence replace the leader sequence of native human GAA. Van Bree et al includes no such teaching. Accordingly, withdrawal of the rejection is in order and same is requested.

Prior to turning to the Examiner's rejections based on obviousness, Applicants again direct attention to the fact that the present invention results, at least in part, from studies designed to test the hypothesis that chimeric lysosomal polypeptides containing an alternative signal peptide could increase the secretion of lysosomal polypeptides from transduced cells and enhance receptor-mediated uptake of lysosomal polypeptides in tissues. As evidenced by the data presented in the application and in a publication by Applicants (Sun et al, Mol. Ther. 14:822 (2006) – of record), replacement of the lysosomal signal peptide (which targets the polypeptide to the lysosome) by other signal peptides, increased secretion from cultured cells (see, for example, Fig. 15 of the application). Further, receptor mediated uptake of the chimeric polypeptide occurred efficiently (see, for example, Table 1 of Sun et al, Mol. Ther. 14:822 (2006)). It is important to note that the uptake was inhibited by mannose-6-phosphate thereby implicating the involvement of mannose-6-phosphate receptors.

Applicants, not the art, showed that secreted lysosomal proteins (as exemplified by hGAA) demonstrate normal migration on Western blot analysis, consistent with unaltered

glycosylation and processing of the chimeric protein. Importantly, the normal glycosylation is observed, despite the increased secretion and presumably shortened residence in the Golgi (see Example 14). Nothing in the art upon which the Examiner relies would have suggested that such would be the case.

Turning now to the Examiner's rejections based on obviousness, claims 3, 4, 73-75 and 77-79 stand rejected under 35 USC 103 as allegedly being obvious over Amalfitano et al in view of Heus and Haseltine et al. The rejection is traversed

The failing of Amalfitano et al is discussed above. Nothing in the teachings of Heus relating to 3' untranslated region sequences of GAA or in Haseltine et al's teaching of the albumin signal sequence would have cured that deficiency. Further, it is submitted that the documents upon which the Examiner would only have been combined by one having benefit of the present invention. Accordingly, the rejection is not well founded and withdrawal of same is requested.

Claims 1-3, 5, 7-18, 21-29, 73-75 and 77-79 stand rejected under 35 USC 103 as allegedly being obvious over Amalfitano et al in view of Heus and further in view of Martin et al. The rejection is traversed.

Again, the failings of Amalfitano et al are discussed above. Nothing in the teachings of Heus relating to 3' untranslated region sequences of GAA or in Martin et al's teaching of an erythropoietin signal peptide the albumin signal sequence would have brought one skilled in the art closer to the claimed invention. Further, it is submitted that the documents cited here, like those cited above, would only have been combined by one having benefit of the present invention. Accordingly, reconsideration is requested.

Claims 1-3, 5, 7-18, 21-29 and 73-79 stand rejected under 35 USC 103 as allegedly being obvious over Amalfitano et al in view of Heus and further in view of Whitfeld et al. The rejection is traversed.

The fundamental deficiency of Amalfitano et al is discussed above. Nothing in the teachings of Heus relating to 3' untranslated region sequences of GAA or in Whitfeld et al's teaching of an α-1-antitrypsin secretory signal sequences would have cured the failing of the primary reference. Further, it is submitted that the documents cited here, like those cited above, would only have been combined by one having benefit of the present invention. Reconsideration is requested.

Claims 1-3, 5, 7-18, 21-29 and 73-79 stand rejected under 35 USC 103 as allegedly being obvious over Amalfitano et al in view of Heus and further in view of Meulien. The rejection is traversed.

The deficiency of Amalfitano et al is described above. Nothing in the teachings of Heus relating to 3' untranslated region sequences of GAA or in Meulien's teaching of a Factor IX secretory signal sequence would have cured the failings of Amalfitano et al. Further, the documents cited here, like those cited above, would only have been combined by one having benefit of the present invention. Reconsideration is requested.

The Examiner is requested to initial and return the PTO/SB/08a Form submitted herewith.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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